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Subclassification of Picornaviruses

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INTRODUCTION

The term "picornavirus" was recently proposed by an International Enterovirus Study Group (48) as a new name for the viruses recovered from man that were formerly grouped together (13) as the enteroviruses (i.e., the poliomyelitis viruses, the coxsackieviruses, and the echoviruses), plus similar newly recognized viruses which have been called Salisbury strains (79), rhinoviruses (1, 4), coryzaviruses (27), muriviruses (51), or enteroviruses (37), by various investigators. It was also proposed that viruses with similar properties which are recovered from lower animals be included in the picornavirus group. The better-known animal viruses which would be included are those responsible for foot-and-mouth disease in cattle and other cloven-footed animals, those causing Teschen disease in swine, Theiler's mouse encephalomyelitis viruses, and encephalomyocarditis virus which infects rodents and a variety of other animals.

The picornaviruses were defined (48) as viruses which (i) are small in size (15 to 30 mμ in diameter), (ii) are insensitive to inactivation by ethyl ether, and (iii) contain ribonucleic acid (RNA) cores. The proposal of the International Study Group was accepted (5) by the International Subcommittee on Viral Nomenclature and probably will be widely used in the future.

The picornavirus group as defined above contains a large number of distinct serotypes (probably 100 or more infect man alone) and includes the etiological agents of a number of important diseases of man and animals. Because of the large number of distinct viruses involved, there is an obvious need for a generally accepted method of subdividing the group for practical purposes. Unfortunately, there has not been unanimity of opinion on how this can be best accomplished.

POLIO, COXSACKIE, AND ECHOVIRUSES

Considering first those picornaviruses recovered exclusively from man, the first serotypes to be recognized (beginning in 1908) were those which can usually be recovered by the intracerebral inoculation of monkeys. These were the three viruses responsible for most cases of poliomyelitis in man, and there was an obvious parallel between the method of isolation, the lesions produced in the central nervous system of lower primates, and those which occur naturally in man.

With the introduction of the infant mouse as a host system for virus isolation, a large group of previously unrecognized picornaviruses was uncovered. These were named the Coxsackie viruses (16) in 1949 (from the name of the town in New York where the first isolates were obtained), and they were subdivided (17) into serotypes causing only general myositis in infant mice (called group A), and those inducing focal myositis along with lesions in various other organs (called group B). These two groups together now consist of approximately 30 serotypes. The term "coxsackie" was chosen to provide a name that was without anatomical or clinical connotations, because too little was originally known of the pathogenesis of human infections to justify a descriptive term. It was soon found that certain serotypes of the group A coxsackieviruses were the etiological agents of the disease known as herpangina (33) and others of group B were responsible (15) for epidemic myalgia or pleuro-

dynia (Bornholm disease). It was learned eventually, however, that coxsackieviruses of both groups (as well as the poliomyelitis viruses) could cause aseptic meningitis syndromes which were clinically indistinguishable from each other. Later, it was shown that at least one virus, first designated as coxsackie group A type 7, could be isolated either by the intracerebral inoculation of monkeys or by the intraperitoneal inoculation of infant mice, and that this virus could induce fatal paralytic disease in man which was clinically identical to poliomyelitis (82). Because of these pathogenic effects, certain investigators designated this agent as poliomyelitis virus type 4 (11). Thus, consideration of only the poliomyelitis viruses and coxsackieviruses makes it obvious that there is an imperfect correlation between the classification of picornaviruses in these subgroups and the type of disease which they produce under natural conditions in man.

The introduction of cell culture techniques for virus isolation resulted in the discovery of the next large group of previously unrecognized picornaviruses, which were designated ECHO viruses in 1955 by a committee of American workers (12). With one exception, all these are now considered to belong in the picornavirus group. However, it should be pointed out that the original criteria for inclusion of a virus in the ECHO (enteric cytopathogenic human orphan) subgroup were not those now used for the picornaviruses. In fact, the only essential criteria were (i) that the virus be cytopathogenic for primate cell cultures and not pathogenic for infant mice; (ii) that it be recovered from the human alimentary tract and infect man; and (iii) that it not be related to other groups of viruses recoverable from the human alimentary tract. Originally, there were no criteria for echoviruses with respect to size, ether resistance, or type of nucleic acid—the three essential requirements for a picornavirus. Only one virus, echovirus type 10, was originally labeled as an echovirus and is not now included in the picornavirus group. Echovirus type 10 is now classified (68) as reovirus type 1 on the basis of its larger size and other important biological properties which distinguish it from the other echoviruses. The original homogeneity of the echovirus group is largely explained by the fact that other groups of viruses which are commonly present in the human alimentary tract, and which are recognizable by presently used cell culture techniques, were already known when the echovirus category was established. For example, if the adenoviruses had not previously been described, a number of adenovirus serotypes would almost certainly have been described as echoviruses. It is well to keep these facts in mind when evaluating the classification of viruses which have been labelled (41) ECMO (enteric cytopathogenic monkey orphan), ECBO (enteric cytopathogenic bovine orphan), etc. The viruses of lower animals have been studied much less intensively than those of man, and it would be surprising if the ECMO, ECBO, etc., categories were eventually found to be as homogeneous as the echovirus category.

With the widespread use of cell culture methods for the isolation of viruses from the human alimentary tract, it soon became apparent that certain viruses with the properties of picornaviruses could not easily be fitted into the category of poliomyelitis virus, coxsackievirus, or echovirus. Thus, strains of one virus, originally described as echovirus type 9, were found after passage in cell culture to induce lesions in infant mice like those produced by group A coxsackieviruses (6). It was also found that some strains of this serotype (72), but not the prototype (6), could be isolated directly in infant mice. Because of the demonstrated pathogenicity for infant mice, this virus was called coxsackievirus group A type 23 by certain workers (72), even though it was known that a serologically identical agent had already been given the designation of echovirus type 9. Thus, the pathogenicity for infant mice of certain strains of this virus was judged by some a more important criterion for classification than the lack of such pathogenicity exhibited by others. Certain other viruses originally described as coxsackieviruses, such as types 9 and 21 of group A (see below), were found to be isolated much more easily in cell culture systems than in infant mice. In fact, many strains of these and other group A coxsackieviruses, as well as many strains of group B coxsackieviruses, cannot be isolated in infant mice at all. To increase the problems of classification, it was found that certain echoviruses and coxsackieviruses other than coxsackievirus A type 7 could produce neuronal lesions in monkeys (19, 46, 83). These viruses have not as yet been isolated directly in lower primates—perhaps because such isolation techniques are no longer widely used.

Proposal of the Term "Enterovirus"

As the data cited above were becoming available, it also became known that the poliomyelitis viruses, the coxsackieviruses, and the echoviruses shared common properties of size and resistance to ethyl ether, as well as origin in the human alimentary tract. In 1957, it was proposed by the same committee that had set up the echovirus category (13) and had designated all the then known serotypes of this subgroup, that the poliomyelitis viruses, the coxsackieviruses, and the

echoviruses be regarded as members of a single family of viruses to be called enteroviruses. It should be noted that the term enterovirus was intended to apply only to certain related viruses recovered from the human alimentary tract and not to any virus which might be found there. Obviously, there were other viruses, such as adenoviruses, which were often recovered from the human alimentary tract and which were not related to the enteroviruses. It is also important to note that it was not specified that enteroviruses were necessarily inhabitants of the lower alimentary tract (intestine) as opposed to the upper alimentary tract (oropharynx). Finally, the use of the term enterovirus was not meant to imply that the viruses so labeled were necessarily involved in disease of the alimentary tract.

In 1962, the committee referred to above proposed a single numbering system for the enteroviruses (49). This was done because it had become more and more apparent that the boundary lines between the previously accepted subgroups were indistinct and that certain strains seemed to belong in one subgroup while other strains of the same immunological type seemed to belong in another. It had become increasingly difficult to assign newly recognized serotypes to one subgroup or another because no one had agreed (or could agree) on the answers to such pertinent questions as the following. (i) What degree of neuronal damage must a virus produce in how many monkeys and by which routes to be called a poliomyelitis virus? (ii) How many blind passages must be made in infant mice before a virus could be excluded from the coxsackievirus category? (iii) If the same virus produces neuronal lesions in monkeys, neuronal disease in man, and coxsackievirus-like lesions in infant mice, is it to be called a poliomyelitis virus or a Coxsackie virus? (iv) If one strain of a virus fits clearly into one subgroup and another strain fits clearly into another, in which subgroup is the virus to be classified? As noted above, confusion had already been created because some investigators called a virus by one subgroup name (i.e., coxsackievirus), whereas other investigators called the same virus by another (i.e., echovirus). Also, additional evidence of the close relationships among subgroups was provided by cross complement-fixation tests with paired human sera (25, 26, 38, 39, 54, 69, 81).

The solution proposed by the committee was that all newly recognized serotypes be given a sequential enterovirus number with no designation of a subgroup. The previously recognized enteroviruses were also to be given enterovirus numbers. But, in these cases, to avoid confusion and to acquaint readers with the existence of a new nomenclature, it was suggested that for some time both the old and the new nomenclature be used concurrently.

By the time that the above proposal was put forth, it was recognized that the diseases produced in man by enteroviruses ranged from severe paralysis and death to "common colds," but that infection was usually at the subclinical level. Moreover, it was known that different enteroviruses, as well as viruses outside the group, could produce the same syndrome, and that the same enterovirus might cause more than a single syndrome. Furthermore, it was known that strains of the same virus type varied in their host range and tissue tropisms, and that these properties could be readily manipulated by laboratory procedures. For these reasons, pathogenicity was not considered a satisfactory basis for classification.

Although the committee which made the above proposal was not international in composition, it had previously assigned serotype numbers to all the echoviruses, and these had been accepted on an international basis. It is very likely that the enterovirus numbering proposal referred to above would also have been accepted on an international basis had it not been for an unusual circumstance. What happened was that the classification of the enteroviruses became involved in the rivalry surrounding the search for the "common cold" viruses.

"Respiratory" Viruses and Disease

To understand properly the situation which developed, it is necessary to digress and consider the nomenclature employed by some investigators concerned with the etiology of acute respiratory disease in man. It has been common practice for many investigators to refer to "respiratory" viruses. This terminology is not meant to indicate that all viruses so labeled are related to each other, but it does imply that they are recovered from the respiratory tract and that they are etiologically associated with acute respiratory disease in man. Usually, it is not stated whether an agent must be found in the respiratory tract exclusively, predominantly, or only occasionally to be considered a "respiratory" virus. Moreover, an exact definition of the respiratory tract is not usually given. "Respiratory" viruses are distinguished by some from "enteric" viruses.

Grossly, the oropharynx is a crossroads of the respiratory and alimentary tracts. Histologically, its epithelium and lymphoid tissue resemble other parts of the alimentary tract more than other parts of the respiratory tract. Most virus isolations in studies of acute respiratory disease in man are made from material collected by

nasopharyngeal or phaaryngel washings or from throat swabs. Each of these methods would recover viruses present in the oropharynx. One might wonder why such viruses might not logically be considered "enteric." The usual explanation given is that "respiratory" viruses are isolated from persons with acute respiratory disease. Aside from the important difficulties of determining whether or not a virus isolated from an individual with a disease was indeed responsible for that disease, the definition of acute respiratory disease is beset with some of the same difficulties as that of "respiratory" viruses. These difficulties again revolve around the question of whether signs and symptoms referable to the oropharynx (e.g., pharyngitis) are to be considered manifestations of respiratory disease. The situation is further complicated by the concept of the "common cold," which some investigators believe is a clinical entity distinct from other forms of acute upper respiratory disease. In general, the "common cold" is said to be characterized by the presence of coryza and the absence of fever. It is difficult for the uninitiated to go beyond this point because most workers who use the expression have not defined it precisely for the others.

PROPOSAL OF THE TERM "RHINOVIRUS"

In 1960, workers at the Common Cold Research Unit located at Salisbury, England, reported (1, 2, 3, 10, 29, 76, 77, 79) that they had discovered a "new group of viruses" (76), the "typical common cold viruses" (1). These were the agents for which they initially proposed the name "Salisbury strains" (79) and later (1, 4), the name "rhinoviruses." It was recognized from the beginning that these resembled enteroviruses in many respects, including size, resistance to ether, and type of cytopathic effect produced in cell cultures. They were said to differ from enteroviruses because they multiplied in the nose (hence the name), were not found in feces, and required special cell culture conditions (an incubation temperature of 33 C, a *p*H near neutrality, and rotation of the cultures) for their isolation. The rhinoviruses were divided into two groups—the "H" strains, which grew only in cell cultures of human origin, and the "M" strains, which also grew in monkey cell cultures.

It was also recognized initially that the "M" strains of rhinoviruses particularly resembled certain viruses (JH and 2060) which had previously been isolated in the United States from cases of mild acute respiratory disease (58, 64, 65). These viruses had been designated as strains of echovirus type 28 (56). Echovirus type 28 was also known to grow best if cell cultures were rolled and if the *p*H of the culture media was maintained near neutrality (7.2 to 7.0; 30, 57). Moreover, no confirmed isolations had been obtained from feces. Essentially, the claim of the Salisbury group for priority in the cultivation of a new group of viruses was based on their contention that echovirus type 28, unlike the "M" strains of rhinoviruses, could be isolated in cell cultures at 36 C. It was suggested (1), however, that if the concept of the rhinoviruses was accepted it might be logical to consider echovirus type 28 as an "aberrant" rhinovirus.

It should be noted that no data have as yet been published to substantiate the contention that the "M" strains of rhinoviruses do differ from echovirus type 28 in this or any other significant biological property. In fact, it has recently been shown that one of the two "M" strains (B632) described by the Salisbury group is so closely related antigenically to echovirus type 28 that it probably should be considered a strain of the latter virus (14, 51, 53).

Using the cell culture conditions first emphasized by the investigators at Salisbury, but another type of cell culture, another group of workers isolated a number of viruses from "common colds," which they labeled "coryzaviruses" (27). It was not made clear, however, exactly what observed differences led them to believe the coryzaviruses might belong in a different category from the viruses isolated at Salisbury. It is now generally agreed that there are no differences between these viruses (28).

Finally, one of the investigators who isolated the prototype strain of echovirus type 28 proposed that enteroviruses, and related viruses which are isolated principally or exclusively from the respiratory tract, and which are associated with respiratory disease, be called "respiroviruses" (50). This same investigator also suggested (to "stay in this game," as he put it; 52) that echovirus type 28 be designated type 1 of a new virus group to be called "muriviruses" (51) (MILD UPPER RESPIRATORY INFECTION VIRUSES).

Despite the statement that rhinoviruses multiply in the nose, no data have as yet been published to substantiate this contention. Moreover, it has not been shown that enteroviruses do not multiply in this location. In regard to the absence of rhinoviruses from feces, it is known that enteroviruses vary in the ease with which they can be recovered from the lower, as opposed to the upper, alimentary tract. In longitudinal studies of children, certain echovirus serotypes were recovered from the oropharynx very rarely, as compared with the frequency of their recovery from feces. Other echovirus serotypes and some poliomyelitis viruses and group B coxsackie-

viruses were recovered with almost equal frequency from both sources (*unpublished data*). It has also been shown that one group A coxsackievirus (type 21) can be recovered far more easily in adults from the oropharynx than from the feces (8, 36, 73).

PROPOSAL OF THE TERM "NANIVIRUS"

After the "discovery" of rhinoviruses at Salisbury, the director of the group there, who was also chairman of the International Subcommittee on Viral Nomenclature, made the following proposal (1). It was proposed that enteroviruses, rhinoviruses, and viruses with similar properties isolated from lower animals be considered subgroups in a virus family designated by the term "nanivirus" (nanus = dwarf) in reference to their relatively small sizes. The use of the term enterovirus for the entire group was rejected because it "implies a habitat in the intestine" and the "rhinoviruses appear to multiply in the nose." As noted above, the use of the term enterovirus by the American committee was never intended to imply a habitat in the intestine alone, but rather in the entire alimentary tract (enteric = enteron = alimentary tract). Moreover, as indicated previously, no data have been published to show that rhinoviruses do multiply in the nose and that enteroviruses do not. The author of the nanivirus suggestion also allowed that there was a "practical" aspect of his proposal. He wrote, "if enteroviruses are claimed to cause respiratory infections, there could arise difficulty in determining the spheres of influence of different laboratories within the virus field."

Another reason which was advanced for rejecting the use of the term enterovirus to include the rhinoviruses was that "any system [would be] confusing which jumbled up viruses causing poliomyelitis, common colds, and pleurodynia in one heterogeneous assemblage" (2). In this regard, it should be noted that the coxsackievirus A subgroup includes viruses which can cause fatal poliomyelitis (type 7), the "common cold" (type 21), herpangina (several types), exanthems (several types), and aseptic meningitis (several types).

In most fields of taxonomy, names are used as symbols and are not taken literally. There is evidence that this concept usually applies with respect to viruses also. For example, measles, distemper, rinderpest, and respiratory syncytial viruses have recently been included in the myxovirus group (5), although the original meaning of this term (affinity for mucins) had not been shown to apply to the new members.

Also, adenoviruses are generally considered to be "respiratory" viruses (22, 34), since some serotypes have been etiologically associated with acute respiratory disease in man. The first types were recovered from human adenoids, and the term adenovirus was selected because of this association with lymphadenoid tissue. A number of the more recently described adenoviruses have been recovered from the lower alimentary tract and, unlike the previously known serotypes, are rarely, if ever, recovered from the oropharynx (67). Moreover, they have not been shown to have any relationship to lymphadenoid tissues. These viruses are not known to cause any disease in man, although two serotypes produce malignant tumors when inoculated into infant hamsters (35, 75). If the same logic were applied to the adenoviruses as has been applied to the picornaviruses, one or more subgroups should be set up for these viruses. As yet, no such subgroups have been proposed. One wonders what would have been suggested in the way of nomenclature had the adenoviruses which are recovered primarily from the lower alimentary tract been recognized before those serotypes which are associated with respiratory disease and which can be readily recovered from the oropharynx. It is not hard to imagine that one might have heard familiar arguments about the confusion of mixing up adenoviruses of entirely different habitat and pathogenicity. Apparently, it is the association with respiratory disease which is important to some in virus taxonomy.

INTERNATIONAL ACTION

In August, 1962, an International Enterovirus Study Group met in connection with the 8th International Congress of Microbiology in Montreal. This followed the publication of the suggestions of the American committee for the sequential numbering of enteroviruses and those of the chairman of the International Subcommittee on Viral Nomenclature with respect to the terms rhinovirus and nanivirus. As noted above (48), the International Study Group suggested the term picornavirus (pico = small, rna = type of nucleic acid) as a group name for the small, ether-resistant, RNA viruses, in lieu of the proposed nanivirus. No reason was given for this preference.

The International Study Group rejected the proposal of the American committee because it was believed that such a system "would minimize much of the benefit gained from the rich virological and clinical literature in this field." Why this would result from the proposal in question is not clear, since the American committee suggested (49) that both the old and new nomenclature be used concurrently for previously described viruses.

The following subgroups of picornaviruses were recognized by the International Study Group:

A. Picornaviruses of human origin
   1. Enteroviruses
      a. polioviruses
      b. coxsackieviruses A
      c. coxsackieviruses B
      d. echoviruses
   2. Rhinoviruses
   3. Unclassified

B. Picornaviruses of lower animals

It is pertinent to note that the International Study Group neglected to define the subgroups which it sanctioned, and it also did not comment on, or resolve, some outstanding problems of classification (e.g., coxsackievirus A type 7—poliomyelitis virus type 4; echovirus type 9—coxsackievirus A type 23). It should also be noted that the classification approved implied that the differences between enteroviruses and rhinoviruses are greater or more important than those among the subgroups of the enteroviruses (i.e., polioviruses, echoviruses, etc.). No reason was given for this decision. Presumably, it was made on the basis of the alleged differences in habitat.

The International Study Group did recognize the problem created by assigning antigenically identical variants of the same virus to more than one subgroup and the confusion created by shifting a virus from one group to another as its strains became more fully characterized. It was felt that these difficulties could be overcome by the following procedure.

"New antigenic types would be placed in a temporary unclassified subgroup until other strains of the same antigenic type, preferably isolated from different areas of the globe and in different years, had been studied so that the biological properties of the type would be sufficiently well known to permit a representative prototype strain to be selected and assignment made to a proper subgroup in the classification.

"Unclassified picornaviruses will include distinct antigenic types which cannot be clearly classified into one of the above groups. This may be (a) because only a single strain is known, and past experience has shown that one cannot be sure that isolates from other places and at other times will have the same properties; or (b) because the known properties of the new antigenic type are not clearly distinctive for subgrouping purposes. In any case, such a picornavirus will be placed in the unclassified subgroup and given a type number, as 'picornavirus, unclassified type 1, 2, 3, 4, 5. . . .' After an unclassified type becomes reassigned to its proper subgroup, then its unclassified type number will never be reused."

In effect, this would mean that most of the newly recognized picornavirus serotypes would be placed in the unclassified category, since newly recognized viruses are usually described from one or more strains isolated in the same year and in the same locality. Also, as noted above, the International Study Group failed to define the subgroups and, hence, the newly recognized serotypes would have to remain in the unclassified category until the subgroups were defined. Thus, in essence, the International Study Group proposed a solution similar to that of the American committee except that the term picornavirus was used instead of enterovirus, and the original subgroup names were retained for the serotypes already described. The proposals of the International Study Group were promptly accepted by the International Subcommittee on Viral Nomenclature (5).

ACTION OF THE AMERICAN COMMITTEE

Subsequently, the American committee attempted to follow these proposals and proceeded to assign the terminology "unclassified picornavirus types 1–6" to six candidate strains (37). Five of the viruses had been isolated by use of the techniques first emphasized by the investigators at Salisbury. All six viruses had been awaiting designation for some time in anticipation of the decisions to be made in Montreal. The American committee also added the designation "U.S." after the type numbers to indicate that this was not an international decision (there being no international mechanism for reviewing candidate strains at the present time).

A short note embodying this action, unanimously approved by the American committee, was submitted to, and accepted for publication in, an American scientific journal. As a courtesy, the chairman of the International Subcommittee was sent a copy of this paper before publication. The following events then took place. The chairman of the International Subcommittee wrote the American committee that he opposed its use of the unclassified picornavirus category for viruses that appeared to be rhinoviruses. Thus, while he welcomed the "blessing" given by the International Study Group to his proposal of the rhinovirus subgroup, he was not personally prepared to accept (despite the official acceptance of his own Subcommittee) the mechanism proposed to avoid the assignment of variants of the same virus to more than one subgroup (i.e., the assignment of a new antigenic type to the unclassified subgroup until strains had been isolated in different geographic areas and in different years).

Shortly after this exchange of communications, the editor of the journal referred to above wrote the American committee that he had de-

cided to reverse his decision concerning its paper which had previously been accepted and which was about to appear in print. The reason given for this action was that the journal was establishing a policy of not accepting papers suggesting changes or additions to virus nomenclature unless they were official publications of internationally recognized bodies. It was not stated why the journal had suddenly decided to institute this policy at this particular time.

In view of the formidable opposition, the note by the American committee was eventually rewritten, omitting reference to unclassified picornaviruses, and submitted to another journal where it was eventually published (47). By this time, three additional picornavirus serotypes had been characterized and included. Four of the newly recognized viruses were given the designation of echoviruses (although this term was still not defined), and five were designated rhinoviruses (see below).

DEFINITION OF RHINOVIRUSES

When the International Subcommittee on Viral Nomenclature accepted the proposals of the International Enterovirus Study Group, it appointed an *ad hoc* committee (of two persons) to "clarify its decision that certain viruses recently isolated from colds and similar diseases in man should be gathered into a subgroup of the picornaviruses to be called rhinoviruses." This was done, and a description of the rhinoviruses has been published (78). The *ad hoc* committee decided that echovirus type 28 was a bona fide rhinovirus and that it was the first of the subgroup to be isolated. The *ad hoc* committee also decided that it was "not possible or desirable to distinguish [rhinoviruses] from enteroviruses on the basis of the disease they cause or the cultures in which they grow." However, it concluded that "it is desirable to separate rhinoviruses from enteroviruses because typical members of each group vary in so many ways." It did not state how the "typical" enteroviruses and rhinoviruses were selected for comparison. Groups of viruses within the enterovirus category also differ from each other in many ways.

Despite the many ways in which enteroviruses and rhinoviruses were said to differ, only one criterion was found by which rhinoviruses and enteroviruses could be separated from each other with any degree of assurance. This was the acid-stability test. Rhinoviruses were said to be inactivated in fluids with a *p*H between 3 and 5 and enteroviruses were not. This is not an "all-or-none" phenomenon, because it was subsequently reported (7) that some infectivity of rhinoviruses remains, even at *p*H 3, if the initial titer is high. It is of interest to note that the only criterion (acid-stability) that can now be used to separate rhinoviruses from enteroviruses was discovered (20, 42) after the term rhinovirus had been proposed and after it had been accepted by the International Subcommittee on Viral Nomenclature.

PROBLEMS OF IMPLEMENTATION

It is generally agreed that within the large picornavirus family there appear to be subgroups of viruses which resemble each other in various ways more than they do other serotypes. It is also generally agreed that, for the most part, these subgroups appear to merge imperceptibly into each other.

There are at least two specific reasons why it would be desirable, if possible, to establish defined subgroups within the picornavirus family. One of the reasons is that it would simplify the task of identifying isolates by reducing the number of serotypes with which they had to be compared. The other reason is that if an isolate of a previously unknown serotype could be classified in a known subgroup one might gain a number of clues as to its probable cultural characteristics, disease relationships, epidemiology, etc.

It will be noted that the subdivision sanctioned by the International Subcommittee is, in essence, the historical one based largely on the pathogenicity of the viruses for various hosts. Thus, the poliomyelitis viruses could be loosely defined as those viruses which produce disease of the central nervous system in primates, the coxsackieviruses as those pathogenic for infant (but not adult) mice, the echoviruses as those which are not pathogenic for either of these hosts, and the rhinoviruses (originally) as those which cause "common colds" in man. Aside from the fact that pathogenicity is difficult to define and to measure, and that it is known to be one of the most variable characteristics of a virus, there are other difficulties with this system of classification. One obvious objection is that the categories are not mutually exclusive. For example, a virus which is pathogenic for infant mice may also be pathogenic for the central nervous system of primates (e.g., coxsackievirus A type 7). Another difficulty is that at least some of the categories thus defined (e.g., the group A coxsackieviruses) will not be particularly homogeneous with respect to cultural characteristics, disease relationships in man, or epidemiology—properties which make subgrouping desirable. This state of affairs could almost be predicted of a subgroup such as the echoviruses (now consisting of at least 30 serotypes) which need share only the property of

being nonpathogenic for infant mice and the central nervous system of primates.

It has been argued (1) that, despite the fuzzy boundaries between the proposed picornavirus subgroups, they are still useful concepts, just as the grouping of stars into constellations has been useful to astronomers. There are benefits (such as the conservation of well-known names) that would derive from such an approach to picornavirus classification. However, the disadvantages of such a system far outweigh the advantages.

To begin with, virologists apparently are not content to leave viruses in the "constellations" where they were first described, but insist on shifting known viruses from one "constellation" to another, or creating new ones as additional data become available. This leads to a multitude of names for the same virus, and is, to say the least, confusing.

Secondly, attempts to use information derived from the described constellations can be very misleading. The history of Coe virus is a good example. This virus was isolated from the throat washings of a patient with acute respiratory disease and described in 1958 as an apparently newly recognized virus (45). It was subsequently recovered from adults with acute respiratory disease in widely separated geographic areas and was shown to cause "common colds" in volunteers (8, 24, 36, 43, 55, 59, 73, 80). In 1961, it was discovered (70) that Coe virus was identical with coxsackievirus A type 21 which had been described (72) in 1959, but which actually had been isolated at least 4 years earlier. The prototype of this latter virus had been isolated in the same laboratory in which Coe virus had been isolated. The prototype strain of coxsackievirus A type 21 was recovered from the feces of a patient with paralytic poliomyelitis (poliomyelitis virus type 1 was also isolated from the same patient). Apparently, Coe virus was not originally compared with the isolate which became the prototype of coxsackievirus A type 21 because the latter, unlike the former, could be adapted to serial passage in infant mice and produced myositis in these animals. It is also possible that the investigators might have been influenced by the fact that strains of Coe virus had been isolated from throat washings of adults with acute respiratory disease and that the prototype of coxsackievirus A type 21 had been isolated from feces (where it was present as a "fellow traveler").

It is fortunate, in view of the problems of classification which have already been discussed, that man apparently does not share many picornaviruses with lower animals. The picornaviruses of lower animals which have been reported to infect man are the viruses of foot-and-mouth disease (23), a virus recently isolated from horses (61, 62, 63), and encephalomyocarditis virus (40). In the case of each of these viruses, it appears that man is infected only rarely and is a dead end in the transmission chain.

Although the problems of subdividing the picornaviruses of lower animals will not be discussed at length, it is pertinent to note that the *ad hoc* committee (78) which drew up the description of the rhinoviruses applied this term to an acid-labile virus which was isolated from the nasal secretion of a calf with acute rhinitis (9). It was thus implied that the subgrouping officially sanctioned for picornaviruses of human origin could also be used for those isolated from lower animals. If the acid-stability criterion were applied to picornaviruses isolated from cattle, one would have to include the viruses of foot-and-mouth disease in the rhinovirus category, because they are unstable at *p*H 3 to 5 (66). Consequently, in the case of bovine picornaviruses at least, the criterion of acid-stability does not assure a particularly homogeneous group with respect to clinical manifestations in natural hosts.

The viruses of foot-and-mouth disease are also pathogenic for infant, but not adult, mice and produce marked myositis in these animals (60). They could thus be considered coxsackieviruses. Since at least one picornavirus isolated from the feces of healthy dairy cattle (44) would also have to be included in the coxsackievirus category, one might encounter objections to this latter suggestion from workers interested in foot-and-mouth disease. It is even possible that someone would protest the mixing up of cattle picornaviruses of entirely different habitat and pathogenicity.

It is pertinent that the lesions induced in infant mice by picornaviruses (and which are the basis for the separation of the coxsackievirus A and B subgroups) are apparently not specific for this group. For example, the investigator who named the coxsackieviruses described the lesions produced in infant mice by reovirus type 1 as the same as those caused by coxsackieviruses of the B group (18). This observation was made at the time that reovirus type 1 was still known as echovirus type 10 (see above).

In view of the difficulties which have been cited, what other proposals have been made for subgrouping the picornaviruses? It has been suggested that the picornaviruses of human origin be subgrouped by the disease they produce in man (e.g., the use of the term respirovirus to include picornaviruses causing respiratory disease in man; meningovirus for those frequently associated with aseptic meningitis, etc.; 51). Such

a classification is obviously unworkable. It is a very difficult task to determine what disease, if any, a given isolate might cause, because most infections are subclinical. Also, it is well known that many individual picornavirus serotypes can produce more than one type of clinical manifestation.

Picornaviruses can also be subdivided on the basis of differences in plaque morphology (31), in replication in cell cultures of various types and from various species (32), in susceptibility to inhibition by certain chemicals [such as 2-(α-hydroxybenzyl)-benzimidazole (HBB); 21, 74], in cytopathic effects as seen in stained cell cultures (71), and in the presence and characteristics of hemagglutinins (*unpublished data*). Unfortunately, the subdivisions effected by these criteria do not correlate well with each other, with the classical criteria of animal pathogenicity, or with what is known of the clinical characteristics and epidemiology of the various serotypes. However, some of the criteria mentioned are useful in the practical work of identifying picornavirus isolates. As yet, none of them appears particularly useful for purposes of nomenclature.

The subdivision of the picornaviruses proposed by the International Subcommittee is largely unworkable for those who must identify isolates and describe new serotypes. At the present time, there appears to be no practical alternative for these purposes but to consider the serotypes of the picornavirus family (at least those of human origin) on an individual basis. The easiest way to do this would be to number them sequentially as picornaviruses. One could then consider more readily a number of the properties of each serotype in trying to predict its cultural characteristics, clinical importance, and epidemiology in relationship to other serotypes. For example, one could have picornavirus "x" which is acid-stable, pathogenic for infant mice, insensitive to inhibition by HBB, etc. Admittedly, this is not as easy as remembering only that virus "x" is a coxsackievirus, but it is apt to be more useful and less misleading. Sequential numbering seems to be working satisfactorily with another large heterogeneous group, the adenoviruses.

In contrast to what is sometimes claimed, the subdivision proposed by the International Subcommittee increases the number of facts which must be remembered by clinicians concerned with picornaviruses. For example, clinicians would have to remember such facts as which particular group A coxsackieviruses cause respiratory disease, which group B coxsackieviruses do so, which echoviruses do so, which rhinoviruses do so, etc. If sequential numbering were used, one would have to remember only that picornaviruses "X," "Y," "Z," etc., had been shown to cause respiratory disease. In both systems, one would have to remember former names for the same virus (e.g., echovirus 28 = rhinovirus "x"). In the case of the sequential-numbering proposal, multiple names would not be created in the future.

SUMMARY

In subdividing a large heterogeneous group of viruses, such as the picornaviruses, decisions must be made as to the relative importance of various viral characteristics for purposes of classification. It is desirable that such decisions be made on as logical a basis as possible, so that the resulting classification will have the widest possible utility. In the case of the picornaviruses, some of the proposals made for subdividing the group seem to have been unduly influenced by proprietary considerations, and the use of these proposed schemes has resulted in a certain amount of confusion. Decisions arrived at by an international group attempting to satisfy conflicting points of view do not necessarily result in a workable system of classification.

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